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INCLUSION COMPOUNDS

By MAXIMO BARON*

For many years, a large number of compounds were known that seemed to exist either in more than one crystalline form or combined with others in a manner that could not be explained by conventional ideas. Pfeiffer (1) first attempted to explain this situation by applying Werner's co-ordination theory. His chief contribution was to call attention to a new class of "molecular compounds" that seemed to contain bonding of a different kind from that resulting from the normal chemical reactions. Thus, the choleic acids, β-quinol, cyclodextrin derivatives, and others were included in the general class of molecular compounds.

This situation remained unchanged until urea adducts were discovered by Bengen (2) while working on pasteurized milk. Further work disclosed general principles that could be applied to elucidate the nature of some of the ill-named molecular compounds. Most important of all, it laid the groundwork for the investigation of a new class, the "inclusion compounds" (Schlenk's "Einschlussverbindungen") (1).

Definition

Inclusion compounds do not arise from the linkage of two reactants by means of covalent or co-ordinate bonds, but from the ability of one compound spatially to enclose another. The enclosed compound ("guest") is in a situation whereby it cannot readily leave its position, although it is not actually bonded to the including compound ("host"). The most essential property of the latter is its ability to form a solid structure containing hollow spaces (some will not do it when pure) within which the prospective guest can fit. The resulting "compound" will then be stable, because any deficiency in actual bonding energy will be compensated for by the effect of close spatial fitting.

Inclusion compounds, then, are combinations of complete organic molecules that are united spatially, leaving unaffected the bonding systems of the components. In general, it cannot be predicted whether or not a molecule will be able to crystallize in such a form as to leave adequate hollow spaces to be occupied by a guest. The only exceptions are those compounds that have a ring-type structure (e.g., cyclodextrins) in which the spatial arrangement necessarily leaves a hollow space in the center.

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Very little can be said, in general, about the forces of interaction involved in the formation of inclusion compounds, since the requirements are different for each type. It has been shown, however, that, whenever two components are physically close to one another, which is the case in the formation of inclusion compounds, the normally weak van der Waals forces are of considerable importance (3).

Inclusion compounds can be classified as follows (4):

1. Polymolecular inclusion compounds:
   (a) Those with channellike spaces.
   (b) Those with cagelike spaces (the clathrates).
2. Monomolecular inclusion compounds.
3. Macromolecular inclusion compounds.
4. Products of the blue iodine reaction.

Polymolecular Inclusion Compounds

This type includes all those compounds that result from the introduction of a variable number of molecules of a guest into the crystalline framework formed by molecules of the host. Two subtypes can be recognized, considering the nature of the space available for inclusion, since it may take the form either of channels or of cages.

A. With Channellike Spaces.—In these compounds, the host (urea, thiourea, desoxycholic acid, etc.) can accommodate any of a variety of guests. When, in the presence of a suitable guest, a host compound is allowed to crystallize, it will come out in a lattice containing roughly cylindrical channels of a specific diameter, the nature of the guest molecule being varied only insofar as it will not have a cross section incompatible with the diameter mentioned. The framework of the pure host differs from that in the adduct, thus making it impossible to determine in advance whether or not it will form such adducts.

Although the restrictions in cross section of the guest are narrow, the lengthwise requirements are more lenient; there is a minimum length for the chain, but practically no maximum. The distribution of the chains along the channel is completely statistical. In this type of inclusion compound, there is no simple molar ratio of host to guest.

1. *Urea Adducts.*—By x-ray diagrams, it has been shown that pure urea obtained by crystallization from a solvent forms a rather loose tetragonal crystalline lattice that is stabilized through hydrogen-bonding (1). When urea is crystallized from a solution which contains unbranched hydrocarbon chains, the solid obtained has a hexagonal lattice that seems to be more compact and firm. This is an indication that the host compound cannot crystallize in a compact structure without the help of its prospective guest. X-ray pictures show the existence of a central channel of 5-A. diameter; this provides ample space for any straight paraffin chain (4) possessing only those substituents that will not change its cross section. Thus, a hydrogen atom can be replaced by a fluorine atom which is of the same approximate size, but not by the larger bromine atom. In some cases, a side chain has a marked influence; for example, benzene forms no adducts, whereas alkylbenzenes with chains longer than *n*-octadecyl are readily included.

Urea adducts are formed by simply mixing urea with the long-chain component; this can be done in the solid form or by using some suitable solvent (e.g., chloroform or methanol) (3, 5). The formation of these adducts is exothermic (0.8 to 1.3 kcal. per mole). They are solids and are stable at room temperature. They do not have clear-cut melting points, but decompose so that the melting point observed is that of

urea (1). The minimum requirements in chain length are given in Table I (1). These adducts can be decomposed by heat or by solvents, a property of considerable practical utility. Within the channels of the adduct, the guest is protected from external influences. Unsaturated fatty acids thus become stabilized to oxidation.

Table I. Urea Adducts

Guest Compounds	Lowest Useful Member
Hydrocarbons	*n*-Hexane
Alcohols	Hexanol
Ketones	Acetone
Acids	Butyric
Halides	Octyl
Amines	Hexamethylenediamine

2. *Thiourea Adducts.*—The complexes of thiourea with inorganic salts were already known when Angla (6) showed that molecular compounds were also obtainable. Generally speaking, thiourea adducts are similar to those of urea, the main difference being that the channels in the crystalline structure have a larger diameter (7 A.). As a result, unbranched hydrocarbon chains are too slender to promote formation of the crystalline structure of the adducts. On the other hand, the more bulky compounds, such as those with branched chains, here take the place held by the *n*-paraffins in the urea adducts.

Typical guest compounds are trimethylpentane, cyclopentane, decalin, bicycloparaffins, 2-bromo-octane (this appears to be the only compound having just one substituent that will give an adduct), and chloroform (the smallest compound to give an adduct). One of the largest compounds to give a thiourea adduct is 2,6,9,12,16-

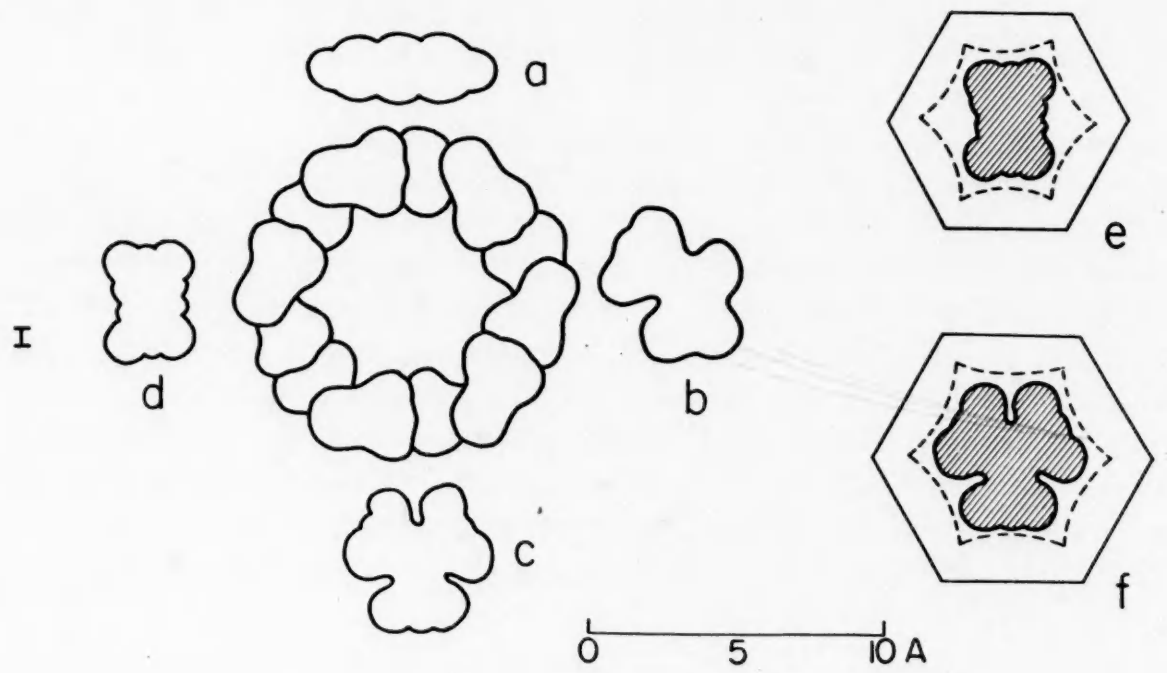

Diagram I shows a crystal of urea with its central channel in comparison with cross sections of four molecules: (a) benzene, (b) a branched hydrocarbon (one side chain), (c) a branched hydrocarbon (several side chains), and (d) an unbranched hydrocarbon. Cross sections of adducts from urea and thiourea (e and f) are included to show the difference in size.

pentamethylheptadecane, some 22 A. long. Large side chains, however, like ethyl and isopropyl, will prevent addition (1). Another difference between these adducts and the urea adducts is that an irregular force seems to exist in the channels, causing the guest molecules to become irregularly distributed in the channels and not in a head-to-tail contact. This is confirmed by the absence of continuous layer lines in the x-ray diagrams (1).

3. Desoxycholic Acid Adducts.—These are considered to be the oldest of the known inclusion compounds, having been described by Wieland in 1916 (1). It was found that desoxycholic acid formed unusual combinations with fatty acids; these adducts were named choleic acids. Later work showed that their composition depends on the number of carbon atoms of the acid. Thus, up to C_8, four molecules of desoxycholic acid are required; from C_9 to C_{14}, six molecules; and for C_{15} and beyond, eight are required. X-ray diagrams show that each guest molecule is in the center of a channel formed by two sickle-shaped host acid molecules. All of the choleic acids seem to give the same size crystals: 25.8 × 13.5 × 7.23 A.; the value of 7.23 A. for the *c*-axis results from the superposition of two molecules of desoxycholic acid. The bonding here seems to be stronger than usual, since these compounds have a characteristic melting point of 186° C., whereas pure desoxycholic acid melts at 176°-177° C. (1).

In addition to the fatty acids, many other compounds give this type of adduct; for example, acenaphthene, cholesterol, alkaloid (7), xylene, naphthalene, benzaldehyde, and camphor. Since choleic acids dissolve in water without decomposition, this property provides a method of solubilizing fatty acids and insoluble hydrocarbons.

Desoxycholic acid has been used successfully to separate the *d* and *e* components of a racemic mixture of camphor (8).

4. 4,4′-Dinitrobiphenyl Adducts.—The same channel-type adducts are obtained with these compounds, but here the presence of a large number of π-electrons introduces strong electrostatic influences. From an observation of a list of compounds that can act as guests, it is seen that they are markedly nucleophilic (they are mostly 4,4′-disubstituted biphenyls, such as N,N,N′,N′-tetramethylbenzidine, 4,4′-dimethoxybiphenyl, benzidine, 4,4′-dihydroxybiphenyl, biphenyl itself, and others (1). From these considerations, it is evident that the adducts of benzidine and

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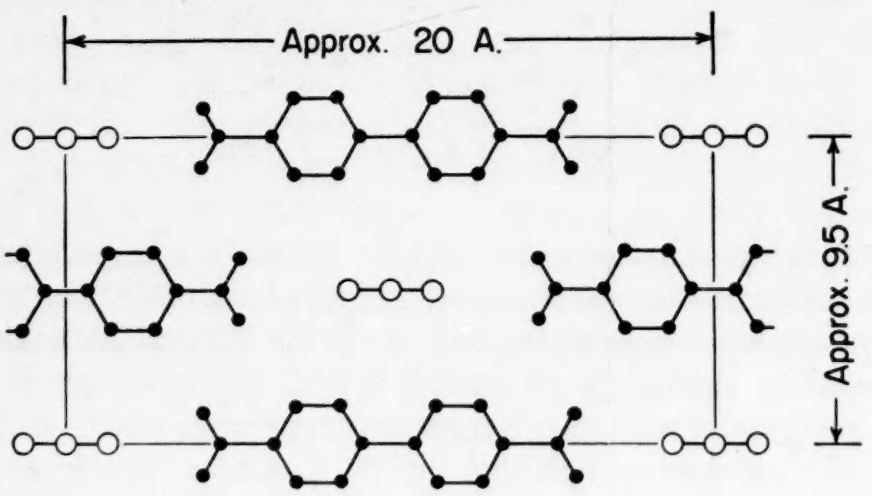

N,N,N′,N′-tetramethylbenzidine will have the highest melting point, since their bonding energies will be the highest. Diagram II shows a cross section of an idealized structure of the dinitrobiphenyl adducts (1).

(To be continued)

References

1. In Cramer, F., "Einschlussverbindungen," J. Springer Verlag, Berlin, Germany, 1954, 115 pp.
2. Bengen, F., Ger. Pat. 869,070 (1953); *Chem. Abstr.*, *48*, 11479 (1954).
3. Cramer, F., *Angew. Chem.*, *68*, 115-120 (1956).
4. Powell, H. M., *Endeavour*, *9*, 154-158 (1950).
5. Zilberstein, G., *Bull. soc. chim. de France*, (5)*18*, D33-D38 (1951).
6. Angla, B., *Ann. chim.*, (12)*4*, 639-698 (1949).
7. Fieser, L. F., and Newman, M. S., *J. Am. Chem. Soc.*, *57*, 1602-1604 (1935).
8. Sobotka, H., and Goldberg, A., *Biochem. J.*, *26*, 905-909 (1932).

POLYPHOSPHORIC ACID

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(Conclusion)

It was erroneously reported in Part I that Stetter and co-workers prepared a fused eight-membered ring by the PPA-catalyzed cyclization of the requisite ω-5,8-dimethyl-6-tetralyl-alkyl acid ($n=5$). Although the PPA-catalyzed cyclization was unsuccessful, the Friedel-Crafts reaction using the acid chloride was employed with a 49% yield of product. Neither method was successfully used in preparing the nine-membered ring ($n=6$).

Beckmann Rearrangement

In the Beckmann rearrangement of ketoximes, PPA proved to be an effective catalyst, giving 90-100% yields of amides from the oximes of many aromatic and heterocyclic ketones (10). Thus, fluorenone oxime, heated several minutes with PPA at 175°-180° C., afforded phenanthridone in 93% yield. Similarly, tetralone-1-oxime provided 91% of homodihydrocarbostyril (10), and the ketoxime of tetrahydro-1,4-thiapyrone (XVII), heated 15 min. with PPA at 115° C., produced 5-keto-4-aza-1-thiacycloheptane (XVIII) in 85% yield (30). However, it has been reported

XVII XVIII

(31) that certain α,α-disubstituted cyclic ketoximes gave unexpected products when a Beckmann rearrangement was attempted with PPA as the catalyst. For example, 2,2-diphenylcycloheptanone oxime, in PPA for 10 min. at 125° C., gave 7,7-diphenylheptamide. Although aldoximes frequently give nitriles under the conditions usually associated with the Beckmann rearrangement, with PPA as catalyst, at least some of them have given high yields of amides (10). For example, *n*-heptaldoxime, heated with PPA at 130° C., furnished 92% of *n*-heptamide. In general, PPA seemed to cause less isomerization and degradation of aldoximes than did other catalysts.

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*References for the Kennard article appeared only in Vol. 29, No. 1 *Bulletin*.

Miscellaneous Uses

In the hydrolysis of nitriles to amides, PPA, being a mild acid, gives higher yields of amide with less accompanying hydrolysis to acids (6). Simple aliphatic and aromatic nitriles are hydrolyzed to the corresponding amides in about 1 hr. at 110° C. Thus, *o*-tolunitrile gives *o*-toluamide in 95% yield.

Certain amines and carboxylic acids readily formed the corresponding amides in the presence of PPA (6). The yield of amide increased as the amine basicity decreased. Thus, although aniline proved unreactive, *p*-nitroaniline gave 67% of *p*-nitroacetanilide and 2,4-dinitroaniline gave a 92% yield of 2,4-dinitroacetanilide.

The Lossen rearrangement of hydroxamic acids is also effectively catalyzed by PPA (6). The reaction is carried out during 5-10 min. at 150°-170° C. In this manner, β-naphthoic acid, with hydroxylamine hydrochloride, gives β-naphthylamine in 82% yield.

The benzyl esters of amino acids have proved extraordinarily useful in the synthesis of peptides, but they have not been available previously from a simple, direct reaction. Recently, Erlanger and Hall (32) reported the direct esterification of the amino acid with benzyl alcohol in the presence of PPA. The reaction was carried out in about 4 hr. at 90°-105° C., and, for the esterification of DL-phenylalanine and L-cysteine, resulted in yields of 65% and 45%, respectively.

The nitration of mono-substituted malonic esters with fuming nitric acid–acetic acid mixtures is reported to be hazardous, because of the potentially uncontrollable exothermic reaction which occurs at higher temperatures. The substitution of PPA for acetic acid in this mixture allows the use of 60° C. temperature and reduces the

$$RCH(CO_2C_2H_5)_2 \longrightarrow RC(CO_2C_2H_5)_2 \\ | \\ NO_2$$

risk involved (33). In the instance, where R is cyclohexyl, the yield is only about 15%, but, when R is isopropyl, isobutyl, *n*-butyl, and *n*-decyl, yields of 60, 78, 75, and 97% are recorded.

The bromination of aliphatic carboxylic acids in PPA has been found to be a useful procedure for the preparation of α-bromo acids (34). The acid was heated in PPA (with *ortho*-phosphoric acid as a diluent, if desired) until solution was effected, after which bromine was added. It has been suggested that the brominatable species is a mixed anhydride between the carboxylic and phosphorous acids. After reaction of the bromine, the mixed anhydride was cleaved thermally (direct distillation of the product from the reaction mixture) or was hydrolyzed by pouring the reaction mixture into water. This reaction, which generally led to 60-87% yields and obviated the necessity of using phosphorous, may be illustrated by the preparation of a 76% yield of 1-bromocyclohexane-carboxylic acid from cyclohexane-carboxylic acid in PPA at 120° C. for 10 min., followed by treatment with bromine.

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